Docket No.: 826.1335C

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of:

Kensaku IMAI, et al.

Serial No. 09/785,269 Group Art Unit: 1631

Confirmation No. 2896

Filed: February 20, 2001 Examiner: John S. Brusca

For: METHOD AND APPARATUS FOR AUTOMATICALLY REMOVING VECTOR UNIT IN DNA BASE SEQUENCE

RESPONSE

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

Responsive to the July 19, 2002 Office Action, having an October 19, 2002 due date, reconsideration is respectfully requested based on the following amendments and remarks.

A Petition for a two-month extension of time until December 19, 2002 and a $400.00 large entity fee are included herewith.

I. AMENDMENTS

A. In the Written Description (37 C.F.R. §1.121(b))

Please AMEND the Written Description as follows:

On page 2, first full paragraph, please amend as follows:

The DNA having the composition called a polynucleotide strand is formed by a strand of the above listed four bases, that is, the adenine A, guanine G, cytosine C, and thymine T, bound in a series. For example, if a DNA is extracted from the chromosome in the cell of a human being and is arranged as a sequence, it can be as long as 1 meter and contain 3 billion bases.

01/07/2003 WPHILLIP 00000004 193935 09785269

On page 2, second full paragraph, please amend as follows:

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Thus, a DNA has a strand of bases, that is, a base sequence linked in the form of a strand. The strand is normally very long. In genetic engineering, a DNA including various

genes is cleaved for gene recombination, and a DNA fragment having specific genetic information is extracted from a number of the cleaved DNA fragments. The extracted DNA fragments, that is, object DNA fragments, should be normally proliferated.

On page 6, third full paragraph, please amend as follows:

FIG. 3 shows the vector used in the DNA cloning process and the multiple cloning site in the vector. A number of restriction enzyme sites to be cleaved by various restriction enzymes is concentrated in the multiple cloning site.

On page 7, second full paragraph, please amend as follows:

Recently, computer technology has been utilized as one of the sequence methods, thereby enabling an enormous volume of data to be input and accumulated. Thus, computers are required in determining the base sequence.

On page 11, second paragraph, please amend as follows:

A vector unit base sequence removing method according to the invention is used for removing a vector unit base sequence from a DNA base sequence which is obtained as a result of performing a cloning process by integrating an object DNA fragment into a vector, and includes the vector unit base sequence as a part of a base sequence of the vector and the object DNA fragment. The method includes the steps of: generating a retrieval base sequence as a retrieval key for use in retrieving the vector unit base sequence from the DNA base sequence based on the vector, a restriction enzyme used to cleave the vector for cloning the cloning process, and a restriction enzyme used to obtain the object DNA fragment; specifying the vector unit base sequence using the retrieval key; and removing the specified vector unit base sequence to specify the object DNA fragment.

On page 12, first paragraph, please amend as follows:

The retrieval key may include a forward (leading) retrieval key and a backward (following) retrieval key for respectively identifying areas before and after the object DNA fragment in the DNA base sequence. The forward and backward retrieval keys may indicate the base sequences corresponding to restriction enzyme sites including parts of the vector cleaved by a restriction enzyme for the cloning process and ends of the object DNA fragment.

On page 12, last paragraph extending over to page 13, please amend as follows:

B7 The method according to the present invention may further include the steps of: performing homology retrieval on condition that a similarity value indicating a matching rate between the retrieval base sequence and the DNA base sequence is equal to or larger than a predetermined value in retrieval using the retrieval key for the DNA base sequence; and obtaining a candidate for a base sequence at a junction between the vector in the DNA base sequence and the object DNA fragment according to a result of the homology retrieval.

On page 13, first paragraph, please amend as follows:

B8 The method according to the present invention may further include the steps of: generating a second forward retrieval key by adding to the forward retrieval key a portion that should be existing before the multiple cloning site of the vector; performing a second homology retrieval on condition that a second similarity value indicating a matching rate between a base sequence corresponding to the second forward retrieval key and a base sequence including a base sequence at a junction of the DNA base sequence is equal to or larger than a predetermined value; and obtaining as a vector unit candidate for the vector unit base sequence an area specified as a result of the second homology retrieval and an area or areas before the specified area.

On page 13, last paragraph extending over to page 14, please amend as follows:

B9 The method according to the present invention may further include the steps of: generating a second backward retrieval key by adding to the backward retrieval key a portion that should be existing after the multiple cloning site of the vector; performing a second homology retrieval on condition that a second similarity value indicating a matching rate between a base sequence corresponding to the second backward retrieval key and a base sequence containing the base sequence at the junction of the DNA base sequence is equal to or larger than a predetermined value; and obtaining as a vector unit candidate for the vector unit base sequence an area specified as a result of the second homology retrieval and an area or areas after the specified area.

On page 14, last paragraph extending over to page 15, please amend as follows:

B10 The method according to the present invention may further include the steps of:

generating a second forward retrieval key by adding to the forward retrieval key a portion that should be existing before the multiple cloning site of the vector; generating a second backward retrieval key by adding to the backward retrieval key a portion that should be existing after the multiple cloning site of the vector; performing a second homology retrieval on condition that a second similarity value indicating a matching rate between a base sequence corresponding to the second forward retrieval key and a base sequence including a base sequence at a junction of the DNA base sequence is equal to or larger than a predetermined value, and a third similarity value indicating a matching rate between a base sequence corresponding to the second backward retrieval key and a base sequence including the base sequence at a junction of the DNA base sequence is equal to or larger than a predetermined value; obtaining as a forward vector unit candidate for the vector unit base sequence a forward area specified as a result of the second homology retrieval and an area before the forward area; and obtaining as a backward vector unit candidate for the vector unit base sequence a backward area specified as a result of the second homology retrieval and an area after the backward area.

B10 cont

On page 15, last paragraph extending over to page 16, please amend as follows:

A vector unit base sequence removing device according to the invention is for removing a vector unit base sequence from a DNA base sequence which is obtained as a result of performing a cloning process by integrating an object DNA fragment into a vector and includes the vector unit base sequence as a part of a base sequence of the vector and the object DNA fragment. The device includes: a first unit for generating a base sequence as a retrieval key for use in retrieving the vector unit base sequence from the DNA base sequence based on the vector, a first restriction enzyme used to cleave the vector for the cloning process, and a second restriction enzyme used to obtain the object DNA fragment; a second unit for specifying the vector unit base sequence using the retrieval key; and a third unit for removing the specified vector unit base sequence to specify the object DNA fragment.

B11

On page 16, first full paragraph, please amend as follows:

The device according to the present invention may further include: a vector list storage unit for storing a vector list; and a restriction enzyme list storage unit for storing a restriction enzyme list. The vector is specified in the vector list, and the first and second restriction enzymes are specified in the restriction enzyme list.

B12

On page 16, second full paragraph, please amend as follows:

C13 The device according to the present invention may further include a display unit. The vector may be specified in the vector list displayed on the display unit, and at least one of the first and second restriction enzymes may be specified in the restriction enzyme list displayed on the display unit.

On page 16, last paragraph extending over the page 17, please amend as follows:

C14 The device according to the present invention may further include a program storage unit for storing at least one of: a program for generating the retrieval key by controlling the first unit; a program for specifying the vector unit base sequence by controlling the second unit; and a program for removing the vector unit base sequence by controlling the third unit.

On page 21, after the seventh paragraph, please amend the heading as follows:

Description of the Preferred Embodiments

On page 21, last paragraph extending over to page 22, please amend as follows:

C15 FIG. 5 is a block diagram showing the functions of an automatic vector unit removing method of the automatic vector unit removing method of the present invention. In general, the vector, for example, a circular plasmid DNA molecule, is cleaved, and an object DNA fragment is integrated into the cleaved portion in a cloning process. The automatic vector unit removing method according to the present invention removes the base sequence of a portion of the vector unit contained in the object DNA fragment from the object DNA fragment retrieved from the vectors generated through the DNA cloning process.

On page 25, first full paragraph, please amend as follows:

C16 FIG. 6 is a flowchart showing the basic process of the automatic vector unit removing method according to the present invention. As shown in FIG. 6, the method includes steps S6 through S9. In step S6, the type of the vector used in the cloning process is selected from the vector list and entered. In step S7, the restriction enzyme used in the cloning process is selected from the restriction enzyme list and entered. In step S8, a retrieval key is generated based on the information about the vector and restriction enzyme, and the vector unit is retrieved according to the retrieval key. That is, the homology between the retrieval key and the multiple cloning site is checked, and the vector unit specification program is executed to

select the vector unit. In step S9, the vector unit specified by the vector unit specification program is removed, thus terminating the process.

On page 28, last paragraph, extending over to page 29, please amend as follows:

After the used vector is selected and the multiple cloning site and the restriction enzyme information are extracted in step S13 in FIG. 7, in steps S14 through S17, four restriction enzymes used in cleaving the DNA strands at the 5' and 3' are selected according to extracted information. The selection is made by specifying used restriction enzymes from the restriction enzyme list shown in FIG. 11. FIG. 11 shows a list of the restriction enzymes used when PUC 18 is selected as a vector. The restriction enzyme list stores the restriction enzymes for use in cleaving the restriction enzyme site in the multiple cloning site of the vectors.

On page 29, second full paragraph, please amend as follows:

FIG. 12 is a flowchart showing the vector unit specification and deleting program in step S18 shown in FIG. 7. This process includes steps S21 through S25.

On page 36, first full paragraph, please amend as follows:

If it is determined in step S31 that the single-stranded area on the object DNA fragment 5' side is not located on the 5' side (no in S31), and if it is determined in step S32 that the base sequences of the single-stranded area do not match each other even if the single-stranded area exists (no in S32), then it is determined in step S34 that the restriction enzyme has been mistakenly selected, and control is returned to the restriction enzyme selecting process, thereby repeating the process.

On page 38, first full paragraph, please amend as follows:

FIG. 16 is a flowchart showing the process of determining the retrieval key on the 3' side. Since the flowchart is almost the same as that for the 5' side as shown in FIG. 15, the detailed explanation is omitted here. Steps S40 through S49 shown in FIG. 16 correspond to steps S30 through S39 in FIG. 15. If the single-stranded areas of the restriction enzyme sites to be located on the vector 3' side and object DNA fragment 3' side are actually located on the 5' side, then [F2A] + [F2B5] + [V2C] is defined as the retrieval key on the 3' side. If the single-stranded areas on the 3' side do not exist, then [F2A] + [V2C] is defined as the retrieval key on the 3' side. If the single-stranded areas exist on the 3' side, then [F2A] + [V2B3] + [V2C] is

defined as the retrieval key on the 3' side.

On page 39, last paragraph extending over to page 40, please amend as follows:

FIG. 18 is a flowchart showing the process of retrieving the primary candidate for the boundary on the 5' side using the 5' side retrieval key shown in FIG. 17. When the process starts as shown in FIG. 18, the homology retrieval is performed in the base sequence of the object clone using the 5' side retrieval key in step S51. The retrieval keys and retrieval results obtained as areas indicating a homology exceeding a predetermined value (the number of bases matching in, for example, 6 bases) are listed as primary candidates for boundary portions in step S52, then terminating the process.

On page 45, second full paragraph, please amend as follows:

The methods and processes described above can be realized using an automatic control device such as a computer. As shown in FIG. 25, the control device according to the invention includes a processing device 10, memory 20, display 30, input unit 40, and data reading device 50.

Also, attached is a "Version With Markings to Show Changes Made", comprising a marked-up version of the changes made to the Written Description. 37 C.F.R. §1.121(b)(3).

B. In the Claims (37 C.F.R. §1.121(c)(1)(i))

Please CANCEL claims 23, 32-38 and 41 without prejudice or disclaimer.

Please AMEND claims 24, 25, 26, 28, 29, 31, 39 and 40 as follows:

24. (TWICE AMENDED) A method for analyzing base sequence data and removing, based on said data, a vector base sequence from a recombinant DNA base sequence, comprising:

storing data identifying each of restriction enzymes and data of base sequences at a plurality of restriction enzyme sites of a plurality of vectors correspondingly, in a database;

searching base sequence data of a recombinant DNA obtained by splicing an object DNA fragment into a vector;

obtaining the base sequence data at a front restriction enzyme site and the base sequence data at a back restriction enzyme site, as specified by corresponding to a

restriction enzyme used for cleaving the vector and a restriction enzyme used for obtaining the object DNA fragment, from the database;

generating a first forward retrieval key using the obtained base sequence data of the front restriction enzyme site and a first backward retrieval key using the obtained base sequence data of the back restriction enzyme site;

retrieving base sequence data of the recombinant DNA obtained by a search using the first forward and first backward retrieval keys, and specifying a junction between the vector and the object DNA fragment;

removing the vector base sequence at the specified junction,

wherein sequence data of the first forward retrieval key and of the first backward retrieval key are generated by base sequence data of the vector entered in a vector database, data of a multiple cloning site in the vector, and data of a restriction enzyme site in the multiple cloning site,

wherein data of a forward base sequence from a cleaving point in the restriction enzyme site in the multiple cloning site of the vector are acquired from the database, and a second forward retrieval key is generated using the acquired forward base sequence data of the cleaving point of the restriction enzyme site of the vector,

performing first homology retrieval on condition that a first similarity value between retrieval base sequence data of the recombinant DNA and the first forward and first backward retrieval keys is equal to or larger than a predetermined value,

obtaining a candidate for a base sequence at the junction between the vector and the object DNA fragment according to a result of the first homology retrieval, and

performing a second homology retrieval on condition that a second similarity value between base sequence data of a plurality of first candidates for the junction, and base sequence data of the second forward retrieval key, is equal to or larger than a predetermined value.

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25. (AS ONCE AMENDED) A method for analyzing base sequence data and removing, based on said data, a vector base sequence from a recombinant DNA base sequence, comprising:

storing data identifying each of restriction enzymes and data of base

sequences at a plurality of restriction enzyme sites of a plurality of vectors correspondingly, in a database;

searching base sequence data of a recombinant DNA obtained by splicing an object DNA fragment into a vector;

obtaining the base sequence data at a front restriction enzyme site and the base sequence data at a back restriction enzyme site, as specified by corresponding to a restriction enzyme used for cleaving the vector and a restriction enzyme used for obtaining the object DNA fragment, from the database;

generating a first forward retrieval key using the obtained base sequence data of the front restriction enzyme site and a first backward retrieval key using the obtained base sequence data of the back restriction enzyme site;

retrieving base sequence data of the recombinant DNA obtained by a search using the first forward and first backward retrieval keys, and specifying a junction between the vector and the object DNA fragment;

B24 Cont

removing the vector base sequence at the specified junction,

wherein the sequence data of the first forward retrieval key and of the first backward retrieval key are generated by base sequence data of the vector entered in a vector database, data of a multiple cloning site in the vector, and data of a restriction enzyme site in the multiple cloning site,

wherein forward base sequence data of a forward cleaving point of the restriction enzyme site of the vector, and backward base sequence data of a backward cleaving point of the vector are acquired from the database, and a second forward retrieval key and a second backward retrieval key are generated using the base sequence data of the acquired forward and backward base sequence data of the cleaving points, respectively,

performing a first homology retrieval on condition that a first similarity value between retrieval base sequence data of the recombinant DNA and the first forward and first backward retrieval keys is equal to or larger than a predetermined value,

obtaining a candidate for a base sequence at the junction between the vector and the object DNA fragment according to a result of the first homology retrieval, and

performing a second homology retrieval on condition that a second similarity value between base sequence data of a plurality of first candidates for the junction,

and base sequence data of the second forward retrieval key, is equal to or larger than a predetermined value.

26. (AS ONCE AMENDED) The method according to Claim 25, wherein the sequence data of the first forward and first backward retrieval keys are generated by base sequence data of the vector entered in a vector database, data of a multiple cloning site in the vector, and data of a restriction enzyme site in the multiple cloning site, and

wherein the second homology retrieval is performed using both the second forward and second backward retrieval keys.

28. (TWICE AMENDED) A method for analyzing base sequence data and removing, based on said data, a vector base sequence from a recombinant DNA base sequence, comprising:

storing data identifying each of restriction enzymes and data of base sequences at a plurality of restriction enzyme sites of a plurality of vectors correspondingly, in a database;

searching base sequence data of a recombinant DNA obtained by splicing an object DNA fragment into a vector;

obtaining the base sequence data at a front restriction enzyme site and the base sequence data at a back restriction enzyme site, as specified by corresponding to a restriction enzyme used for cleaving the vector and a restriction enzyme used for obtaining the object DNA fragment, from the database;

generating a first forward retrieval key using the obtained base sequence data of the front restriction enzyme site and a first backward retrieval key using the obtained base sequence data of the back restriction enzyme site;

retrieving base sequence data of the recombinant DNA obtained by a search using the first forward and first backward retrieval keys, and specifying a junction between the vector and the object DNA fragment;

removing the vector base sequence at the specified junction,

wherein backward base sequence data from a cleaving point in a multiple cloning site of the vector corresponding to the restriction enzyme are acquired from the

database, and a second backward retrieval key is generated using the acquired backward base sequence data of the cleaving point,

C26 Cont

performing a first homology retrieval on condition that a first similarity value between retrieval base sequence data of the recombinant DNA and the first forward and first backward retrieval keys is equal to or larger than a predetermined value;

obtaining a first candidate for a base sequence at a junction between the vector and the object DNA fragment according to a result of the first homology retrieval; and

performing a second homology retrieval to identify at least one area in the vector on condition that a second similarity value between base sequence data of a first candidate for the junction, screened by using the first retrieval keys, and base sequence data of the second backward retrieval key is equal to or larger than a predetermined value.

29. (TWICE AMENDED) The method according to Claim 28,

C27

wherein said vector base sequence is removed, when only one area is specified by the second homology retrieval.

30. (AS ONCE AMENDED) The method according to Claim 25, further comprising:

obtaining, as a forward vector unit candidate for the vector base sequence, a forward base sequence selected by the second homology retrieval, and a base

C28

sequence before said forward base sequence; and

obtaining, as a backward vector unit candidate for the vector base sequence, a backward base sequence selected by the second homology retrieval, and a base sequence after said backward base sequence.

31. (TWICE AMENDED) The method according to Claim 30,

wherein said forward vector unit candidate and said backward vector unit candidate are removed from the recombinant DNA base sequence, when there is only one

C29

candidate respectively for the specified forward and backward base sequences, and the specified forward and backward base sequences do not overlap each other.

39. (TWICE AMENDED) A device for analyzing base sequence data and removing, based on said data, a vector base sequence from a recombinant DNA base sequence, obtained as a result of performing a cloning process by integrating an object DNA fragment into a vector, comprising:

a database storing data identifying each of restriction enzymes, and data of base sequences at a plurality of restriction enzyme sites of a plurality of vectors correspondingly;

an obtaining unit obtaining base sequence data at a front restriction enzyme site and base sequence data at a back restriction enzyme site, as specified corresponding to a restriction enzyme used for cleaving the vector and a restriction enzyme used for obtaining the object DNA fragment, from the database;

B30 a generation unit generating a first forward retrieval key using the obtained base sequence data of the front restriction enzyme site, and a first backward retrieval key using the obtained base sequence data of the back restriction enzyme site;

a retrieving unit retrieving base sequence data of the recombinant DNA obtained using the first forward and first backward retrieval keys, and specifying a junction between the vector and the object DNA fragment; and

a removal unit for removing the vector base sequence at the specified junction,

wherein each of said first forward and first backward retrieval keys includes sequence data including an end portion of the object DNA fragment and sequence data including an end portion of the vector base sequence, and specifies a candidate for the junction between the vector base sequence and the object DNA fragment,

wherein a second retrieval key, including sequence data longer than that of said first forward and first backward retrieval keys, is generated, and the junction is specified using the second retrieval key.

40. (TWICE AMENDED) The device according to Claim 39,

B31 wherein said object DNA fragment is specified by removing the junction and base sequence distal to the junction and the object DNA fragment from the DNA base